REMARKS

Claims 1-14 are pending in the instant case and are under consideration. Claim 1 has been amended. APPENDIX A sets forth a version of amended claim 1 with markings to show the changes to the claim. No claims have been cancelled. Accordingly, claims 1-14 will remain pending after entry of the instant amendment.

Claim Rejections – 35 USC § 112

The Examiner has rejected claims 2-3 under 35 U.S.C. 112, second paragraph as being indefinite over the recitation of the term "severity". In particular, the Examiner states that the term "severity" renders "acute migraine" indefinite because the meets and bounds of the term "severity" are not defined. Applicant traverses.

It is Applicant's position that the meaning of term "severity" is clear to one of skill in the art. When discussing the "severity" of a migraine in the specification, reference is made to either moderate or severe migraines. Subjects treated for acute migraine are initially rate the severity of their headaches and associated migraine symptoms on a scale of 0-3 (a four grade headache rating developed by Western New England Headache Clinic (see the specification at Tables I, II, V and VII, as well as at page 3, lines 17-18; page 6, lines 12-13; and page 10, lines 12-15). Accordingly, the specification provides a standard for ascertaining the severity of a migraine, *i.e.*, an art-recognized standard developed and used routinely by neurologists. In view of the teachings of the specification, it is Applicant's position that the term severity is clear to the skilled artisan. Reconsideration and withdrawal of the rejection of claims 2-3 under 35 U.S.C. 112, second paragraph, is respectfully requested.

Claim Rejections – 35 USC § 103

Claims 1-14 stand rejected under 35 U.S.C. § 103 as being unpatentable in view of Welch and Walser. The Examiner relies of Welch for teaching "the administration of 800mg valproate

daily for migraine headache therapy". The Examiner relies on Walser for teaching that valproate can be administered by intravenous injection in 800 mg dosage. The Examiner relies on the combined teachings and concludes that claims 1-14 are obvious. Applicant traverses.

Applicant and Applicant's attorneys greatly appreciate the Examiner's availability for the interview held February 11, 2003. In that interview, the prior art rejection of record was discussed. In the instant Amendment and Response, Applicant has amended the claims of the invention to indicate that the claimed methods are specifically for the treatment of acute migraine (versus prophylactic migraine therapies). In particular, claim 1 has been amended to recite that the method is *for the abortive treatment of acute migraine headache*. Applicant has amended the claim to recite *abortive* treatment - meaning the treatment of an already existing migraine headache in the subject (*i.e.*, a subject having a migraine attack). The abortive treatment of acute migraine featured in the instant claims is clearly distinguishable over the teachings of Welch and Walser, either alone or in combination.

Welch reviews drug therapies for migraine. It is clear by the organization of the Welch reference that there are two distinct topics being reviewed, namely the "Symptomatic Treatment of Acute Migraine" and the "Prevention of Migraine". In Table 1, entitled "Drug Treatment of Migraine Attacks" there is a list of medications that are used to treat and stop a migraine headache after the headache has begun. *i.e.*, acute treatments. These are clearly medications for use after an attack has begun (*e.g.*, for use 'after the fact' of the headache's beginning), hence the sections title, "Treatment of Acute Migraine". This is quite a different group of medications, and quite a different concept from prevention or prophylaxis. Just as prevention of a disease is a quite different challenge from acute treatment once the disease has become manifest, so too, is the difference between acute treatment for migraine and prevention.

It is clear that medications listed in Table 1 on page 1477 of Welch are very different from those reviewed in section 2 of the reference, entitled "Prevention of Migraine" and listed in Table 2 on page 1480. The use of a medication, at a constant or 'steady-state' level to prevent an

occurrence of a migraine, is very different from the acute administration of a high dose, acute 'rescue' medication for the treatment of acute migraine pain and the associated disabling symptoms of nausea, photophobia and phonophobia. The preventative drugs in Table 2 are not used by physicians for acute migraine therapy. Conversely, the acute migraine therapeutics are ineffective for migraine prophylaxis. In particular, valproic acid listed as a "Drug(s) to Prevent Migraine" is nowhere mentioned in the list of "Drug Treatment of Migraine Attacks."

The 800-1000 mg daily oral dosage of valproic acid listed in Table 2 is given as a twice-daily dose orally for prevention of migraine. This drug, by attaining circulating steady-state levels following daily usage for a week or more, can prevent migraine headache. In fact, since Dr. Welch published the 1993 NEJM article, sodium divalproax (oral valproic acid) has been FDA approved for the used of migraine prophylaxis. By contrast, sodium divalproax (oral valproic acid) has not been approved for intravenous use. Nor has sodium divalproax (oral valproic acid) been approved for acute migraine treatment. Only sodium valproate is used intravenously, and this is a different compound from sodium divalproax (oral valproic acid). Likewise, sodium valproate has not been demonstrated by a multi-centered, double blind study to be effective for migraine prophylaxis, and is not, at this time, approved for use for migraine prophylaxis. Thus, even within the class of drugs which includes sodium divalproax (oral valproic acid) and sodium valproate (intravenous valproic acid), the two drugs can not be used interchangeably.

Welch lists oral valproate as a migraine prophylactic among a list of other art-recognized prophylactic therapies (Table 2). Welch separately reviews acute migraine therapies (Table 1). The medications listed in the respective Tables work in distinct ways to either prevent migraine or treat acute migraine attack. None of the prophylactic therapies of Welch are used as acute therapies (excepting the general analgesics). Nothing in the teaching of Welch would have suggested to the skilled artisan to substitute the daily oral valproic acid, *i.e.*, sodium divalproax, of Welch with for a bolus intravenous treatment with sodium valproate (intravenous valproic

acid) to arrive at the instant invention. Walser teaches intravenous valproic acid for treating chronic renal failure but nowhere teaches or suggests the use of intravenous valproic acid for other indications.

For at least the foregoing reasons, it is Applicant's position that the Welch and Walser references, either alone or in combination, fail to teach or suggest the claimed invention. Applicants thus respectfully request that the Examiner reconsider and withdraw the rejection of claims 1-14 under 35 U.S.C. §103(a).

SUMMARY

Applicant submits that in view of the above, pending claims 1-14 are in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the examiner is urged to call Applicant's Attorney at (617) 227-7400.

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LAHIVE & COCKFIELD, LLP
Attorneys at Law

By _____
Debra J. Milasincic, Esq.
Reg. No. 46,931
28 State Street
Boston, MA 02109
(617) 227-7400
(617) 742-4214

APPENDIX A

VERSION WITH MARKINGS TO SHOW CHANGES

1. (Amended) A method [of treating] for the abortive treatment of acute migraine headache in an subject comprising administering to the subject an effective dose of intravenous valproate such that acute migraine headache is lessened or reduced in said subject.